UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/092,208	03/06/2002	Michael C. Pirrung	5405.274	8603

20792 7590 07/26/2004

MYERS BIGEL SIBLEY & SAJOVEC
PO BOX 37428
RALEIGH, NC 27627

EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM.

Office Action Summary	Application No.	Applicant(s)	
	10/092,208	PIRRUNG ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-14 and 16-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-14 and 16-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed May 6, 2004. Currently, claims 12-14, 16-25 are pending.

2. Any objections and rejections not reiterated below are hereby withdrawn.

3. This action contains new grounds of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 12-14, 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pirrung-1 et al. (Bioorganic and Medicinal Chemistry Letters (Vol. 11, pages 2437-

2440, September 2001) in view of Williams et al (Analytical Biochemistry, Vol. 271, pages 194-197, 1999).

Pirrung-1 et al. (herein referred to as Pirrung-1) teaches solid-phase, single nucleotide primer extension of DNA/RNA hybrids by reverse trancriptase. Pirrung-1 teaches that arrays of primers may be used to extent primer-template complexes with labeled dideoxynucleotide termination. Pirrung-1 teaches that "compared to hybridization-based analysis, primer extension methods offer a high signal-to-noise ration and consequent high fidelity. Pirrung-1 teaches that both steps are dependent on the match between primer and template. Pirrung-1 teaches that diagnostic methods that focus on genomic DNA do not take into account effects that transcriptional controls, RNA processing (splicing, editing) or translational controls my have on the transfer of information from DNA to protein. Pirrung-1 teaches that RNA may be a more appropriate means of detecting improperly expressed coding regions (page 2438, col. 1). Pirrung-1 teaches that detection of whether mRNA is present, at what level and in what splice mutant form is important. Pirrung-1 discusses a particular example with he mRNA for aminocyclopropanecarboxylic acid (ACC) synthase (page 2438, col. 2). DNA primers were linked to a solid support via 5' biotin. Pirrung-1 teaches that mRNA was added and hybridization allowed. Primer-template complexes were incubated with AMV reverse trancriptase and ddATP labeled and detected (page 2439, col. 2).

Pirrung-1 does not specifically teach how to design primers for specific detection of alternatively spliced molecules.

However, Williams teaches that alternate splice junctions can be assayed for by using target sequences beyond the first three bases of the splice junction to identify the unique bases (page 194, col. 1). Williams teaches that there is often a complete or partial homology between the bases of the wild-type and the alternative splice junctions (page 194, col. 1). As seen in Table 1, a comparison of primers for targeting two different splice variants is analyzed. The analysis indicates that 5 3' overhang bases is requires for the specific detection. The primers of Williams comprise a 5' common segment for Exon 8 which is about 11 nucleotides in length and the variable primer region is between 3-8 bases. Williams teaches that the "above-described results with targeted primers for ER exon 5 splice variant provide evidence for our earlier hypothesis that a minimum of three of four bases unique to the splice junction in the extreme 3' end of the primer are required to specifically amplify the alternate splice junction. It also appears that in order to design such a primer, the overhang sequences can extend up to eight bases past the splice junction without annealing and amplification of the wild-type sequences (page 196, col. 2). The ER primers were tested for the 6/8 and 4/6 and 1/3 and ¼ splice junctions. Williams suggests that the principles developed in the current study with ER will have broad applicability to splice variants of a diverse range of genes.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the primers of Pirrung-1 for detecting alternatively spliced molecules. While Pirrung-1 specifically teaches that RNA amount, and presence of splice variants found may be detected using RNA/DNA hybrids and

primer extension on an array, Pirrung-1 does not teach how to design the primers and the common and variable primer segments. However, Williams identifies a problem with designing general primers which span the splice sites. Williams teaches that there is often a complete or partial homology between the bases of the wild-type and the alternative splice junctions (page 194, col. 1). Williams teaches that primers may be designed with common segments and variable segments. Williams analyzes in depth two exon junctions to design primers with common and variable segments of varying lengths. Williams ascertains results for each of these splice junctions and applies the technology to two other splice regions to obtain successful results. Therefore, designing primers with a common region to the 5' of the primer and a variable region to the 3' primer was analyzed in detail by Williams to detect splice variants using hybridization analysis. Given the teachings in the art and the strong suggestion by Pirrung-1 to detect splice variants using the APEX based primer extension method, the ordinary artisan would have been motivated to have designed optimal primers for detecting splice variants as specifically taught by Williams.

6. Claims 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pirrung-1 et al. (Bioorganic and Medicinal Chemistry Letters (Vol. 11, pages 2437-2440, September 2001) in view of Williams et al (Analytical Biochemistry, Vol. 271, pages 194-197, 1999) as applied to Claims 12-14, 19-21 above and further in view of Lipshutz (US Pat. 5,856,174).

Neither Pirrung nor Williams specifically teach using mRNA fragments or fragmenting prior to the contacting step.

However, Lipshutz teaches it may be desirable to fragment the sequence prior to hybridization with an oligonucleotide array, in order to provide segments which are more readily accessible to the probes, which avoid looping and/or hybridization to multiple probes. Fragmentation of the nucleic acids may generally be carried out by physical, chemical or enzymatic methods that are known in the art (col. 8, lines 64 to col. 9).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the splice variant detection method of Pirrung-1 in view of Williams by fragmenting the mRNA prior to the contacting step for the explicit benefits taught by Lipshutz. Lipshutz specifically teaches that it is desirable to fragment sequences prior to hybridization with an array in order to provide segments which are more readily accessible to the probes, which avoid looping and/or hybridization to multiple probes. Thus, fragmenting would have been obvious to one of skill in the art at the time the invention was made.

7. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pirrung-1 et al. (Bioorganic and Medicinal Chemistry Letters (Vol. 11, pages 2437-2440, September 2001) in view of Williams et al (Analytical Biochemistry, Vol. 271, pages 194-197, 1999) as applied to Claims 12-14, 19-21 above and further in view of Tocque et al (US Publication 2003/0165931, September 4, 2003).

Neither Pirrung-1 nor Williams specifically teach using a reverse transcripatase having a deleted Rnase H segment.

However, Tocque teaches that a reverse transcripatase devoid of RnaseH activity may be employed because these transcripatese have several advantages. They incrase the yield of cDNA synthesis and avoid any degradation of RNAs which will then be engaged in heteroduplex formation with the newly synthesized cDNA (page 3, para 32).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the splice variant method of Pirrung-1 in view of Williams with the teachings of the benefits of reverse transcripatses that have a deleted Rnase H segment. The ordinary artisan would have been motivated to have used a reverse transcripates that is devoid of Rnase H activity to avoid any degradation of sample RNAs. Thus, modifying the splice variant detection method by using a reverse transcriptase with a recognized benefit would have been desirable to the ordinary artisan.

8. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pirrung-1 et al. (Bioorganic and Medicinal Chemistry Letters (Vol. 11, pages 2437-2440, September 2001) in view of Williams et al (Analytical Biochemistry, Vol. 271, pages 194-197, 1999) as applied to Claims 12-14, 19-21above and further in view of Tarin et al. (US Pat. 5830,646, November 1998).

Neither Pirrung-1 nor Williams specifically teach using CD44 mRNA for splice variant analysis.

However, Tarin teaches metastatic tumor deposits and their corresponding primary tumors over-expressed several alternatively spliced products containing transcripts from exon 11 (co. 7, lines 45-50).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the splice variant detection method of Pirrung-1 in view of Williams by detecting the various well known splice variants of CD44 for the benefit of detecting and analyzing breast tissue sample. The ordinary artisan would have been motivated to have detected CD44 mRNA using array based methods for the purpose of detecting the alternative splice variants associated with cancer.

9. Claims 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pirrung-1 et al. (Bioorganic and Medicinal Chemistry Letters (Vol. 11, pages 2437-2440, September 2001) in view of Williams et al (Analytical Biochemistry, Vol. 271, pages 194-197, 1999) as applied to Claims 12-14, 19-21 above and further in view of Pirrung-2 et al. (Langmuir, Vol. 16, pages 2185-2191, 2000).

Niether Pirrung-1 nor Williams specifically teach generating values for the presence or absence of the exons.

However, Pirrung-2 et al. (herein referred to as Pirrung-2) teaches primer extension assay on microchips for detecting sequences. Pirrung-2 teaches that

primers are formatted into small arrays, specific extension is observed only in the presence of complementary template, with the amount of immobilized primer reflected in the fluorescence signal (abstract). The method of Pirrung-2 requires both a hybridization and extension step which each require and are dependent on matches between primer and template. As seen in Figure, primers are immobilized on a solid support and extension of the primer occurs by hybridization to a template strand and the addition of a labeled terminating nucleotide triphosphate. When primers are arrayed on the surface, the method permits parallel analysis of many sites in analyte DNA (page 2186, col. 1). Pirrung teaches the concept of "two bit" experiments where each oligonucleotide can be represented by a bit (page 2188, col. 2). Pirrung-2 teaches that a code is determined (page 2188, col. 2)(limitations of Claim 23-25). Thus, Pirrung-2 teaches that the signals are very large and robust, particularly in comparison to those obtained from hybridization based DNA chip technologies (page 2189, col. 2).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the data collection means of Pirrung-1 and Williams with the large scale detection means of Pirrung-2 which uses a 2-bit system. The ordinary artisan would have recognized at the time the invention was made that the coded data of Pirrung-2 would allow for multiple templates with multiple primers per site to be examined using a grid. The grid would allow high throughput analysis and data output. Therefore, using the two-bit system of Pirrung-2 would allow faster and more efficient analysis of the multiple exon primers which collectively make up a splice variant.

10. Claims 12-14, 19-21, 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thill (US Patl. 6,632,610, October 14, 2003) in view of Williams et al (Analytical Biochemistry, Vol. 271, pages 194-197, 1999) and further in view of Pirrung-2 et al. (Langmuir, Vol. 16, pages 2185-2191, 2000).

Thill teaches a method of identifying and distinguishing spice variants. As seen in Figure 2 A, an oligonucleotide is designed for O+' and O- which overlap exon boundaries. Thill teaches that one probe of a pair may be specific for the presence of a particular region that is alternatively spliced, whereas the other may be specific for the exclusion of the same region (col. 35, lines 4-10). Thill teaches generation of probes and primers (col. 38). Specifically, probes may be designed to bind specifically to said region, to the junction region between said region and one of the 5' or 3' adjacent region or to the junction between the 5' and 3' adjacent to said regions that are jointed together when said region is deleted. The various probes allow detection of the polynucleotide containing the region and the third type allows detection of the polynucleotide when the region is absent (col. 39, lines 2-12). Thill teaches primers specific of nucleic acid differences may be designed and extension detects presence based upon size (col. 39, lines 22-31). Thill teaches that if the nucleic acid difference consists in replacement of a region with another region, the presence or absence of an amplicon will allow one to determine which exon is present or absent. Thill teaches that different oligonucleotides specific for a given isoform are arrayed on any appropriate support (col. 40, lines 55-59). The assays are then hybridized with different cDNAs and the relative proportions

of each isoform may be measured by the ratio of signal intensity or each oligonucleotide pair (col. 40, lines 65-69). Thill teaches that the nucleic acid sample may comprise nucleic acids obtained from a variety of sources including genomic DNA, cDNA libraries, RNA or tissue samples (col. 38, lines 15-18)(limitations of claim 20).

Thill does not specifically teach using primers which may be detected by extension using at least one labeled base where the primers comprise common segments 8-50 nucleotides and variable segments 2-7 nucleotides.

Williams teaches that alternate splice junctions can be assayed for by using target sequences beyond the first three bases of the splice junction to identify the unique bases (page 194, col. 1). Williams teaches that there is often a complete or partial homology between the bases of the wild-type and the alternative splice junctions (page 194, col. 1). As seen in Table 1, a comparison of primers for targeting two different splice variants is analyzed. The analysis indicates that 5 3' overhang bases is requires for the specific detection. The primers of Williams comprise a 5' common segment for Exon 8 which is about 11 nucleotides in length and the variable primer region is between 3-8 bases. Williams teaches that the "above-described results with targeted primers for ER exon 5 splice variant provide evidence for our earlier hypothesis that a minimum of three of four bases unique to the splice junction in the extreme 3' end of the primer are required to specifically amplify the alternate splice junction. It also appears that in order to design such a primer, the overhang sequences can extend up to eight bases past the splice junction without annealing and amplification of the wild-type sequences (page 196, col. 2). The ER primers were tested for the 6/8 and 4/6 and

1/3 and ¼ splice junctions. Williams suggests that the principles developed in the current study with ER will have broad applicability to splice variants of a diverse range of genes.

Moreover, Pirrung-2 et al. (herein referred to as Pirrung-2) teaches primer extension assay on microchips for detecting sequences. Pirrung-2 teaches that primers are formatted into small arrays, specific extension is observed only in the presence of complementary template, with the amount of immobilized primer reflected in the fluorescence signal (abstract). The method of Pirrung-2 requires both a hybridization and extension step which each require and are dependent on matches between primer and template. As seen in Figure, primers are immobilized on a solid support and extension of the primer occurs by hybridization to a template strand and the addition of a labeled terminating nucleotide triphosphate. When primers are arrayed on the surface, the method permits parallel analysis of many sites in analyte DNA (page 2186, col. 1). Pirrung teaches the concept of "two bit" experiments where each oligonucleotide can be represented by a bit (page 2188, col. 2). Pirrung-2 teaches that a code is determined (page 2188, col. 2)(limitations of Claim 23-25). Thus, Pirrung-2 teaches that the signals are very large and robust, particularly in comparison to those obtained from hybridization based DNA chip technologies (page 2189, col. 2).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the splice variant detection method of Thill with the specific teachings of primer design method of Williams and the labeling and detection methods of Pirrung-2. The ordinary artisan would have been motivated to

have designed the primers of Thill using the guidance taught by Williams. Thill generally teaches that the primers should be designed to overlap different isoform/splice variant junctions to determine whether the junction is present or absent. Thill does not particularly teach the concept of common primer segments and variable primer segments. Williams identifies a problem with designing general primers which span the splice sites. Williams teaches that there is often a complete or partial homology between the bases of the wild-type and the alternative splice junctions (page 194, col. 1). However, Williams teaches that primers may be designed with common segments and variable segments. Williams analyzes in depth two exon junctions to design primers with common and variable segments of varying lengths. Williams ascertains results for each of these splice junctions and applies the technology to two other splice regions to obtain successful results. Therefore, designing primers with a common region to the 5' of the primer and a variable region to the 3' primer was analyzed in detail by Williams to detect splice variants using hybridization analysis. Following analysis of splice variants by designing specific primers to immobilize to the array of Thill, the ordinary artisan would be motivated to have performed a primer extension method as opposed to a hybridization or size based detection method to prevent partial homology between wild-type and alternative splice junctions. Pirrung-2 teaches that methods which rely on both hybridization and primer extension are more sensitive and robust than mere hybridization methods. The ordinary artisan would have been motivated to have further ensured against the misidentification of splice variants based upon hybridization as taught by Williams by modifying the hybridization method of Thill

in view of Williams with a primer extension method would allow for more robust and sensitive detection, as taught in the art by Pirrung-2. Given all of the teachings in the art, the ordinary artisan would have been motivated to have prepared the array based method of Thill using the specific guidance of Williams for the size and lengths of the primers since Williams has optimized the length and design of the primers in alternative splicing detection methods. Further, Pirrung-2 teaches that the method of using primer extension rather than hybridization is more robust and sensitive since it relies on two steps which are dependent on match between primer and template.

11. Claims 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thill (US Patl. 6,632,610, October 14, 2003) in view of Williams et al (Analytical Biochemistry, Vol. 271, pages 194-197, 1999) and further in view of Pirrung-2 et al. (Langmuir, Vol. 16, pages 2185-2191, 2000) as applied to Claims 12-14, 19-20, 23-25 above and further in view of Lipshutz (US Pat. 5,856,174).

Neither Thill, Williams or Pirrung-2 specifically teach using mRNA fragments or fragmenting prior to the contacting step.

However, Lipshutz teaches it may be desirable to fragment the sequence prior to hybridization with an oligonucleotide array, in order to provide segments which are more readily accessible to the probes, which avoid looping and/or hybridization to multiple probes. Fragmentation of the nucleic acids may generally be carried out by physical, chemical or enzymatic methods that are known in the art (col. 8, lines 64 to col. 9).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the splice variant detection method of Thil in view of Williams and in view of Pirrung-2 by fragmenting the mRNA prior to the contacting step for the explicit benefits taught by Lipshutz. Lipshutz specifically teaches that it is desirable to fragment sequences prior to hybridization with an array in order to provide segments which are more readily accessible to the probes, which avoid looping and/or hybridization to multiple probes. Thus, fragmenting would have been obvious to one of skill in the art at the time the invention was made.

12. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Thill (US Patl. 6,632,610, October 14, 2003) in view of Williams et al (Analytical Biochemistry, Vol. 271, pages 194-197, 1999) and further in view of Pirrung-2 et al. (Langmuir, Vol. 16, pages 2185-2191, 2000) as applied to Claims 12-14, 19-20, 23-25 above and further in view of Tocque et al (US Publication 2003/0165931, September 4, 2003).

Neither Thill, Williams or Pirrung-2 specifically teach using a reverse transcripatase having a deleted Rnase H segment.

However, Tocque teaches that a reverse transcripatase devoid of RnaseH activity may be employed because these transcripatese have several advantages. They incrase the yield of cDNA synthesis and avoid any degradation of RNAs which will then be engaged in heteroduplex formation with the newly synthesized cDNA (page 3, para 32).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the splice variant method of Thill in view of Williams and Pirrung-2 with the teachings of the benefits of reverse transcripatses that have a deleted Rnase H segment. The ordinary artisan would have been motivated to have used a reverse transcripates that is devoid of Rnase H activity to avoid any degradation of sample RNAs. Thus, modifying the splice variant detection method by using a reverse transcriptase with a recognized benefit would have been desirable to the ordinary artisan.

13. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Thill (US Pat. 6,632,610, October 14, 2003) in view of Williams et al (Analytical Biochemistry, Vol. 271, pages 194-197, 1999) and further in view of Pirrung-2 et al. (Langmuir, Vol. 16, pages 2185-2191, 2000) as applied to Claims 12-14, 19-20, 23-25 above and further in view of Tarin et al. (US Pat. 5830,646, November 1998).

Neither Thill, Williams or Pirrung-2 specifically teach using CD44 mRNA for splice variant analysis.

However, Tarin teaches metastatic tumor deposits and their corresponding primary tumors over-expressed several alternatively spliced products containing transcripts from exon 11 (co. 7, lines 45-50).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the splice variant detection method of Thil in view of Williams and in view of Pirrung-2 by detecting the various well known

splice variants of CD44 for the benefit of detecting and analyzing breast tissue sample. The ordinary artisan would have been motivated to have detected CD44 mRNA using array based methods for the purpose of detecting the alternative splice variants associated with cancer.

Conclusion

14. No claims allowable over the art.

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Goel et al. (Biotechniques, Vol. 30, No. 5, pages 944-946, 2001) teaches design or primers which span and overlap junctions for exon/exon splice variants.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571) 272-0782.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J. Goldberg

Jeanine Goldberg
Patent Examiner
July 22, 2004